PRM107

EXTRAPOLATING SURVIVAL IN A HETEROGENEOUS PATIENT POPULATION WITH METASTATIC MELANOMA; A CASE STUDY OF INTEGRATING STATISTICAL AND CLINICAL CONSIDERATION

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OBJECTIVES: While the follow-up time on Ipilimumab trials is in excess of 4 years, HTA models often require survival to be extrapolated to 10 years and beyond. However, patient level data on prognostic factors are rarely available; hence extrapolation methods assume a homogeneous study population and are based on statistical considerations only. Such approaches are criticized for disregarding clinical reality and may be biased. In this study a survival extrapolation model that accounted for heterogeneity was developed based on both statistically and clinically relevant considerations. The method was applied on survival data in patients with Metastatic Melanoma. **METHODS:** Survival data were taken from a randomized controlled clinical trial that compared dacarbazine plus placebo versus dacarbazine plus ipilimumab. Two parametric models were explored to extrapolate survival: a model assuming no heterogeneity in patients and another model that divided patients into three subgroups based on cancer stage observed at baseline and additionally included subpopulations of *a priori* unobserved long-term survivors. Survival of the subpopulations was extrapolated and summed to obtain survival in the overall population. Subgroup formation was guided by expert opinion of oncologists. The statistical and clinical validity of the models were assessed. **RESULTS:** Among commonly used distributions (exponential, Weibull, lognormal) the lognormal distribution fitted the survival data best in the no-heterogeneity model whereas Weibull distribution was used for the heterogeneity model. For statistical validity, both models fitted the data reasonably well. However, the no-heterogeneity model underestimated the long tail of the survival curves. The no-heterogeneity model implied decreasing mortality over time while the heterogeneity model implied increasing mortality, which is more clinically relevant. **CONCLUSIONS:** The no-heterogeneity model fitted the data reasonably well but was not relevant for extrapolation from a clinical perspective. The heterogeneity model captured the long tail of the survival curve best, and provided a statistically and clinically relevant model.

PRM108

BIVARIATE INDIRECT COMPARISON META-ANALYSIS MODEL IN ECONOMIC EVALUATION OF CANCER TREATMENTS

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OBJECTIVES: A three-state Markov model for cost-effectiveness analysis of cancer treatments requires information on both progression-free survival (PFS) and overall survival (OS). However, data is not always available on both of these outcomes. The objective of this study is to perform a Bayesian bivariate indirect comparison meta-analysis (BICMA) to obtain estimates of both PFS and OS for use in a cost-effectiveness analysis when data on these outcomes is incomplete. **METHODS:** In a UK Health Technology Assessment report on cost-effectiveness assessment of docetaxel with prednisone/prednisolone for the treatment of hormone-refractory metastatic prostate cancer, a two-state Markov model was specified using OS data from a single randomised controlled trial that did not report PFS. We propose the use of a Bayesian BICMA model that jointly estimates OS and PFS, and which in turn allows for the specification of a three-state Markov model incorporating a post-progression phase. Survival data for the trials included in the BICMA were reconstructed from survival curves, presented in the articles reporting the trials, using the method proposed by Guyot et. al. (*BMC Med Res Methodol* 2012;12:9) using the DigitizeIt and R software. **RESULTS:** The Bayesian BICMA model was designed to jointly model the correlated outcomes: OS and PFS using either non-informative or informative prior distribution on the correlation between the outcomes. An informative prior distribution on the correlation between PFS and OS was based on external evidence using prostate cancer trials presented in Halabi et. al. (*Clin Oncol* 2009;27(17):2766-71). Modelling the correlated outcomes jointly using this bivariate model allows prediction of PFS for the comparison of interest. **CONCLUSIONS:** In the absence of evidence on PFS, required for the specification of a three-state Markov model, the proposed method allows PFS to be constructed thus eliminating the need to reduce the cost-effectiveness analysis to a two-state Markov model.

PRM109

THE DETERMINANTS OF INNOVATION – A BRIEF STUDY OF ISSUES INFLUENCING INNOVATION IN THE PHARMACEUTICAL INDUSTRY

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OBJECTIVES: To examine factors determining the level of innovation in an organisation, examining two factors – market size and the strength of intellectual property rights for a particular drug class **METHODS:** The pharmaceutical industry is used as a case study as it not only relies heavily on R&D, but, with the division between brand name and generic drugs, can provide insight into how the removal of intellectual property rights might affect innovation. The estimation models were based on an economic model for innovation and market size developed by Acemoglu and Linn (2004). Drug approval data obtained from the US FDA was used for the innovation variable; a measure for market size was constructed using prescribed medicines expenditure data from the US Medical Expenditure Panel Survey. The analysis focussed on examining the relationships between the variables using various statistical estimation techniques, starting with a simple OLS log-log model, more general negative binomial and gamma models, as well as fully flexible non-linear smoothing regressions in the form of feed-forward neural networks. **RESULTS:** Brand name approvals increased by 2.64% and generic approvals by 4.2% for a 1% increase in income-based market size. The presence of generic drugs and, thus, weak intellectual property rights did not appear to have a negative effect on research and marketing activity by brand name drugs. Estimates were small, significant, and positive (feed-forward neural networks indicated an even stronger positive relationship between brand and generic approvals), suggesting that the presence of generic drugs might further innovation. **CONCLUSIONS:** It was shown that market size does affect the rates at which pharmaceuticals aim to bring their products to the market. While brand manufacturers react positively to increased market size, weak property rights do not appear to affect innovation output negatively.

PRM110

CROSSOVER ADJUSTMENT IN ONCOLOGY TRIALS USING A RANK PRESERVING STRUCTURAL FAILURE TIME MODEL (RPSFTM): WRAPPING BOOTSTRAPS AROUND ESTIMATES OF LIFE EXPECTANCY FOR CE MODELS

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OBJECTIVES: Oncology trials increasingly permit switching from standard care (SC) to the new treatment following disease progression. Methods to remove the effect of the active treatment in the SC arm are used by HTA agencies to estimate what the effect of the SC would've been had crossover not occurred. One method is using RPSFT models to derive counterfactual survival times without crossover. For CE modeling, these counterfactual survival times need to be parametrically extrapolated to estimate life expectancy. It is known that the RPSFT approach introduces additional uncertainty and e.g. the standard error of a hazard ratio calculated from counterfactual survival times needs to be inflated. Traditional methods of parametric survival analysis don't account for this increased uncertainty which could influence allocation decisions. **METHODS:** A dataset of 400 patients was simulated assuming a Weibull distribution for PFS and OS with 70% of the patients in the SC arm switching after progression. Life expectancy was calculated in two scenarios. In scenario 1 the RPSFTM adjusted OS had Weibull parameter estimates and covariance calculated directly from the counterfactual survival times. In scenario 2 the data was bootstrapped 1000 times. For each iteration a new RPSFT model, associated counterfactual survival times and Weibull functions were fitted. The mean and covariance of these 1000 parameter estimates was taken. **RESULTS:** Mean incremental life expectancy after adjusting for cross-over was the same with and without bootstrapping. When PSA was run, larger confidence intervals in the scenario with bootstrapping indicated, the traditional approach failed to account for the increased uncertainty and underestimated the probability of the new treatment being less efficacious (0.4% without compared to 13.4% with bootstrapping). **CONCLUSIONS:** Failing to appropriately reflect the uncertainty underlying parameter estimates of crossover adjusted survival times could impact HTA decisions when appraisals are based on the likelihood of a treatment being cost effective.

PRM111

THE USE OF DATA FROM PUBLISHED KAPLAN-MEIER SURVIVAL CURVES IN NICE HTAS

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OBJECTIVES: Reporting of survival outcomes from clinical trials is often limited to median survival times, hazard ratios, Kaplan-Meier curves and numbers at risk. The numerical results are not always sufficient for meta-analysis and cost-effectiveness analysis. Further information can be obtained by digitizing and analysing the Kaplan-Meier curves. The most basic analysis approach is to fit a non-linear model to the Kaplan-Meier curve and use this to estimate parameters such as the mean survival time. Methods have recently been developed for estimating individual patient data (IPD) from Kaplan-Meier curves. Once individual patient data is estimated, standard survival analysis approaches can be used to estimate parameters and also provide estimates of uncertainty in the curve fits. The objective of this study was to review the methods commonly used and assess the impact of the improved methods, where IPD is estimated, on the inferences drawn. **METHODS:** We conducted a systematic review of the methods that have been used in NICE HTAs to obtain data from published Kaplan-Meier curves. We examined the frequency of each method, how results were used and any feedback from Evidence Review Groups. Improved methods, estimating IPD, were applied to a selection of studies where this was not conducted in the original analysis. The impact of the improved methods on the conclusions of the studies was assessed. **RESULTS:** The review showed that most HTAs used non-linear models to approximate the Kaplan-Meier curves. It also showed that the improved methods, estimating IPD, can have a significant impact on conclusions drawn from survival results. **CONCLUSIONS:** The estimation of IPD from Kaplan-Meier curves is a valuable method that is currently underutilised. It has the potential to provide better estimates of survival parameters and to improve the characterisation of uncertainty in such estimates. This is especially important when survival curves are extrapolated.

PRM112

A BAYESIAN DYNAMIC MODEL OF ASTHMA IN THE REAL LIFE

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OBJECTIVES: Evolution of asthma disease severity over time can be highly dependent on the prescription patterns and drug compliance of patients. The purpose of the modeling is to analyze longitudinal observational data of cohort of asthma patients to describe and quantify the dynamics of adherence, prescriptions, and outcomes and their interaction over time. **METHODS:** We explored and analyzed 5 different observational studies following asthma patients in France over up to 2 years. Main patients' demographics along with prescriptions, ACT and 3-level GINA control scores could be defined every quarter and exacerbations at a given quarter were adjucated based on hospital admissions. Medication possession ratios could be defined quarterly and used as a proxy for adherence. A patient-

level dynamic Bayesian inhomogeneous Markov model with quarterly time-step was then developed to jointly describe prescriptions and outcomes over time in relation with adherence proxy using medication possession ratio, adjusting for patients demographics and seasonality. Internal and external validation was performed. **RESULTS:** . Such Bayesian model could be fitted to the available data with different parameters informed by one or another data source. Treatment switches were associated with severity at the previous quarter while adherence was significantly improved when patients are switched and when they are less controlled in the previous quarter. Risk of exacerbations was depending on the control score and season at the present quarter and on the risk of exacerbation at the previous quarter. Control was significantly improved by a better adherence and to a lesser extent by a treatment escalation and improved severity at the previous quarter. **CONCLUSIONS:** This Bayesian dynamic model allowed quantifying the most important interactions between drug uses and effects on control and exacerbations over time, hence providing a powerful tool for real-world outcomes predictions in asthma patients.

PRM113

UNCERTAINTY QUANTIFICATION OF LARGE-SCALE HEALTH ECONOMIC SIMULATION MODELS

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OBJECTIVES: Large scale simulation models (e.g. Archimedes Model, MISCAN) are increasingly used to predict cost-effectiveness of medical interventions and to drive reimbursement decisions. These models are complex and involve hundreds of parameters and inputs. Quantification of parameter uncertainties using traditional sampling-based approaches (e.g., Monte Carlo sampling and its variants) can be prohibitively expensive for these models. **METHODS:** We overcome the limitations of traditional probabilistic sensitivity analysis through a 4-step process. First, we conduct a thorough survey of all parameters and their confidence intervals. Second, we use local sensitivity analysis to evaluate the effects of each parameter on the outcome of interest. Third, based on results from single-parameter sensitivity analysis, we rank and identify a group of parameters that have the largest effects on the outcome. We then employ response surface (RS) approximation methods to create a mathematical model of the model predictions for these parameters. We use Latin Hypercube sampling (LHS) to generate data points and multivariate adaptive regression splines (MARS) to build the response surface approximations. Fourth, we sample parameters from their joint distributions, and then use the constructed response surface to calculate the probability distribution of the predicted outcomes. **RESULTS:** We apply the above methodology to quantify uncertainties in predictions of the Archimedes Model for effectiveness of colorectal cancer (CRC) screening by colonoscopy (COLO) and fecal immunological test (FIT). We started out with 200 parameters and identified 20 parameters that have significant influences on predicted effectiveness of CRC screening. We conclude that there is a 89% chance that COLO will save more life years FIT, after accounting for parameter uncertainties. Similarly we estimate that there is a 61% probability that FIT is more cost effective than colonoscopy. **CONCLUSIONS:** We have developed a robust and efficient methodology for quantifying parameter uncertainties of large-scale simulation models used for cost-effectiveness analysis.

RESEARCH ON METHODS – Patient-Reported Outcomes Studies

PRM114

CATALOGUE OF EQ-5D SCORES FOR CHRONIC CONDITIONS IN DENMARK

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OBJECTIVES: EQ-5D catalogues have been developed and tested in US and UK. The current study aims to develop a Danish preference-based EQ-5D 3L scores catalogue for around a hundred of the most common monitored chronic conditions. The development is based on experiences from the US and UK, but adding new factors of importance such as health habits, BMI, social networks and stress. **METHODS:** The marginal disutility estimates will be calculated using CLAD and OLS regression on a single source population from a random sample: the National Danish Health Survey Data from 2010 which is a self-administrated survey with approx. 38.000 respondents age ≥16. The survey data is combined with data from national registers containing individual health data e.g. diagnosed chronic conditions during hospitalization, medication, use of hospitals as well as socio-economic data. The catalogue differs from UK and US catalogues' by adding health habits information and by using ICD-10 classifications from registers as well as it is based on Danish EQ-5D tariffs. The marginal disutility is calculated for each chronic condition controlling for age, gender, ethnicity, income, education and comorbidity etc. **RESULTS:** Marginal disutility estimates (EQ-5D) for around a hundred ICD-10 chronic conditions are presented and compared. It is expected that this new knowledge will contribute and qualify prioritization debate, when results are published and combined with knowledge of for example factors of importance and burden of disease in costs. **CONCLUSIONS:** The catalogue will provide scientist with an "off-the-shelf" tool for use in health economic evaluations. Marginal disutilities estimates can be used to estimate QALY's in CEA for a wide variety of conditions in Denmark.

PRM115

PATIENT PREFERENCES ON TREATMENTS FOR ERECTIL DYSFUNCTION DEFINED BY MEANS OF DIFFERENT ATTRIBUTE GROUPS: THE METHOD OF ADMINISTRATION IS THE MOST VALUED ATTRIBUTE AND THE ORODISPERSIBLE TABLET IS THE MOST PREFERRED LEVEL

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OBJECTIVES: Phosphodiesterase type 5 inhibitors (PDE5i) for the treatment of erectile dysfunction (ED) have similar pharmacologic profile. Patient preferences may influence the outcome of treatment. The objective was to assess patient preferences on treatments for ED by applying Conjoint Analysis. **METHODS:** Seven attributes were selected through a literature review and a consultation with 25 patients treated of ED and 5 experts: effectiveness (E), rapidity of onset (R), duration of effect (D), adverse events (AE), methods of administration (MA), price (P) and interaction with alcohol and food (I). 3 groups of scenarios were selected using "Orthogonal Design": Phase 1, 9 scenarios with 4 attributes (R, D, MA, I); Phase 2, 16 scenarios with the 7 attributes; Phase 3, 9 scenarios with 4 attributes (E, MA, P, I). It was applied the "Order of simulated preference" method by using cards with symbols and text. Interactions of age, comorbidity and frequency of sexual intercourses with preferences were studied. **RESULTS:** The set of 16 scenarios was very difficult for patients. A total of 314 patients participated in Phase 1, 99 in Phase 2 and 178 in Phase 3. Order of preferred attributes: Phase 1: MA (57.99%), D (16.68%), I (14.57%) y R (10.76%); Phase 2: MA (40.53%),E (21.98%), R (8.98%), P (8.11%), D (7.46%), AE (6.67%),I (6.25%); Phase 3: MA (53.9%), I (22.45%), P (12.50%), E (11.14%). The preferred MA in the 3 phases was the orodispersible tablet with reference to pill and injectable. No statistically significant associations were found with age, comorbidity and frequency of sexual intercourse. **CONCLUSIONS:** . Patients gave more importance to the attribute "method of administration" in any of the three phases performed. The preferred MA was orodispersible tablet over pill and injectable.

PRM116

CHOOSING HEALTH STATES FOR ELICITATION OF POPULATION PREFERENCES FOR THE EQ-5D

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OBJECTIVES: The EQ-5D-3L descriptive classification defines a total of 243 health states which presents a problem when seeking to establish social preferences. As it would be challenging to value all 243 health states, a subset is chosen but the basis for this selection varies across national valuation studies. The aim of this study was to choose health states based on the most commonly found health states experienced by the Irish population. **METHODS:** EQ-5D data from four different datasets were combined to determine what health states are prevalent in Ireland. Data from a general population study of health (SLAN), an over 70 population cohort, a rheumatoid arthritis and psoriatic arthritis cohort. The most commonly experienced health states were determined and these were arranged on a 5 dimensional lattice. Health states were chosen using the Manhattan distance metric. **RESULTS:** A total of 12,520 ratings of self-reported EQ-5D health states were included. Fifty two per cent of the cohort had perfect health (11111). Ninety five per cent of states include at least one '1' and no '3'. 126/243 health states were not experienced in these datasets. The Manhattan distance between health states was measured. The imposition of such a metric facilitated the identification of clusters of states and associated centroids. Distance sampling was used to identify states within the clusters. A simple random sampling strategy was also used across the lattice to ensure coverage of health states outside of the cluster **CONCLUSIONS:** Previous population preference elicitation studies have used theoretical approaches to health states elicitation, which could lead to health states being directly valued which are rarely experienced in the population. The approach presented here uses the information already known about the population, to inform choice of health states for population valuation of health using the EQ-5D.

PRM117

HEALTH UTILITIES INDEX (HUI®): POPULATION REFERENCE STATISTICS

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OBJECTIVES: To describe HUI reference statistics available from clinical and general population health studies. **METHODS:** Reviews of published literature, unpublished reports and corporate databases were used to identify summary statistics or data available for calculation of summary statistics. Published examples illustrate the use of HUI reference statistics for health-related quality of life (HRQL) scores to assess the health of patients relative to general populations and of general populations between countries. **RESULTS:** Summary statistics of HRQL scores were compiled from published clinical studies (n=5), population health surveys (n=6), or provided by investigators of individual studies (n=3). Statistics from four sets of published results were used to identify health problems among patients treated for acute lymphoblastic leukemia in childhood in a recently published study. Results from the Joint Canada/US Survey of Health (JCUSH), conducted at the same time in both countries using the same survey methodology are presented here in brief. The mean HUI3 score in Canada (0.88) was slightly higher than in the US (0.87) ($p<0.05$). However, the mean HUI3 score for those with less than a high school education in Canada (0.81) was much higher than the mean for the same group in the US (0.74) ($p<0.05$). HUI Mark2 (HUI2) and HUI Mark3 (HUI3) summary statistics by country, gender, race and age groups are presented in 43 tables on the HUI web-site (www.healthutilities.com). **CONCLUSIONS:** The results highlight the usefulness of continuous preference-based measures of population health such as the HUI3. Population reference data enable international comparisons of population health and provide normative data with which to interpret results from clinical studies. The publicly available summary statistics of interval-scale preference-based measures for the HRQL of reference populations provide valid, reliable and cost-effective results for clinical and general population studies.

PRM118

PATIENT PREFERENCES IN THE CHOICE OF DISEASE MODIFYING DRUGS FOR MULTIPLE SCLEROSIS

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